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Preparation of 2,2,6-Trisubstituted 7-Oxa-1-azabicyclo[2.2.1]heptanes from 4-Nitro-1-butene Derivatives. A Route to 2,2,6-Trisubstituted-4-hydroxypiperidines

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Abstract

4-Nitro-1-butene derivatives **2** readily available from the palladium(0)-catalyzed *C*-allylation of nitroalkanes were converted into 7-oxa-1-azabicyclo[2.2.1]heptane derivatives **5** in three easy steps including an intramolecular 1,3-dipolar cycloaddition reaction of *N*-(3-alkenyl)nitrones. The palladium catalyzed hydrogenolysis of the compounds **5** afforded 2,2,6-trisubstituted-4-hydroxypiperidines. The oxidation of **5** by 3 equiv. of *m*-chloroperbenzoic acid (MCPBA) gave acyclic β-hydroxy-δ-nitroketones **9** in high yield.

Keywords: nitrocompounds; nitrones; cycloaddition; piperidines.

Intramolecular 1,3-dipolar cycloaddition reactions of *N*-(3-alkenyl)nitrones gives 7-oxa-1-azabicyclo[2.2.1]heptane derivatives [1-12] which are readily converted into highly substituted piperidine derivatives under reducing conditions [1, 3-7, 10]. The nitrones necessary for this cycloaddition are prepared from *N*-(3-alkenyl)hydroxylamines and carbonyl compounds [2 -6]. The key problem in this method is the synthesis of the corresponding hydroxylamines, which can be obtained from the sodium cyanoborohydride reduction of oximes of β,γ-unsaturated carbonyl compounds [2, 3] or from the addition of allylboronates to aldoximes [4-6]. In addition *N*-(3-alkenyl)nitrones can be also prepared from (*Z*)-aldoximes by 4-bromo-1-butene alkylation [1, 9, 11] or from Michael addition of 1,3-butadiene derivatives substituted at the 2- and 3-positions with electron-withdrawing groups [7-10].

Since various 4-nitro-1-butene derivatives are readily available from the palladium(0)-catalyzed *C*-allylation of nitroalkanes [13-15] we envisaged that reduction of these compounds should smoothly afford *N*-homoallylhydroxylamines, which could be converted successively into *N*-(3-alkenyl)nitrones and 7-oxa-1-azabicyclo[2.2.1]heptanes. Herein we describe the utility of this approach for the preparation of novel 2,2,6-trisubstituted derivatives of 7-oxa-1-azabicyclo[2.2.1]heptane (Scheme 1), which are difficult to synthesize by reported methods, and

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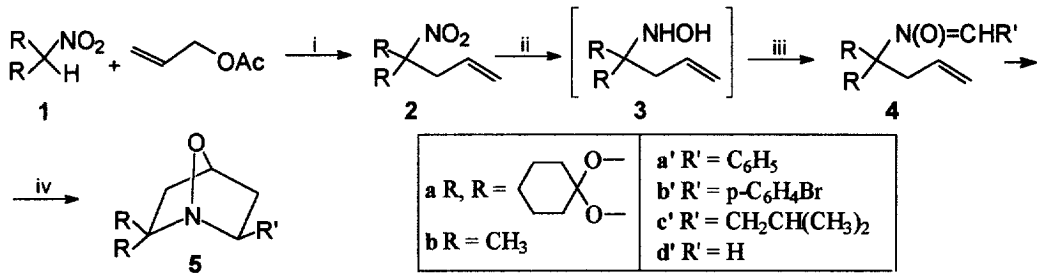
attempts at their conversion into heterocyclic compounds under reducing as well as oxidizing conditions. Moreover, knowing that polyhydroxylated piperidines (azasugars) are powerful inhibitors of various glycosidases [16] we also examined the usefulness of 7-oxa-1-azabicyclo[2.2.1]heptanes for the synthesis of similar compounds. In this aim 2,2-pentamethylene-5-nitro-1,3-dioxane **1a** [17] was employed as starting material.

The allylation of the sodium salts of **1a** and 2-nitropropane **1b** by allyl acetate in methanol in the presence of *tetrakis*(triphenylphosphine)palladium(0), generated *in situ* from *bis*(triphenylphosphine)palladium(II) chloride and triphenylphosphine [13], afforded both allyl derivatives **2a** (m.p. 37-39 °C from hexane)[1] and **2b** [13, 14] in 65% yield (Scheme 1).

Scheme 1



Reagents and conditions: (i) MeOH, MeONa, 5 mol% $Pd(PPh_3)_2Cl_2$, 10 mol% PPh_3, reflux, argon; (ii) MeOH, Zn (4 equiv.), AcOH (5 equiv.), 0-5 °C; (iii) R'CHO (0.85 equiv.), 0-5 °C→r.t., overnight; (iv) toluene, reflux, argon, *ca.*7 h.

The nitrocompounds **2** were reduced to hydroxylamines **3** by zinc-acetic acid system [18, 19] in methanol at 0 °C. When **2** was not detected by TLC the corresponding aldehyde was added and stirring was continued at ambient temperature until the reaction was complete. The crude nitrones **4** were pure enough to be used to the next step without purification, their samples, except **4ad'**, being purified by column chromatography for identification. The 1,3-dipolar cycloaddition of **4** was carried out in boiling toluene to afford the *exo* adducts **5** in good yield (Table 1). The syntheses with 3-methylbutanal proceeded less cleanly than those with the aromatic aldehydes. The *exo* configuration of **5** was determined on the basis of the values of $^3J_{endo5\text{-}6}$ and $^3J_{exo5\text{-}6}$ [1]; $^3J_{endo5\text{-}6}$ (7.5 - 8.5 Hz) was larger by about *ca.* 3 Hz than $^3J_{exo5\text{-}6}$ (4.6 - 5.5 Hz).

Table 1
Yields of the adducts **5**

Compound	Yield [%][a]	m.p. [°C]
5aa'	41	114-115
5ac'	43	oil
5bb'	49	oil
5bc'	26.5	64-66

[a] Calculated on **2**.

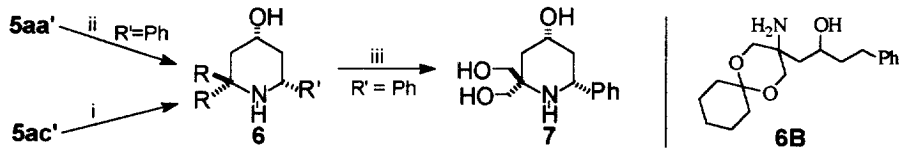
Attempts to prepare the adducts **5** from **3a** and cyclohexanone or formaldehyde were unsuccessful. However, in each case the cause of the failure was different; in the former case the highly substituted nitrone was not produced even during heating at 90 °C (n-propanol) and in the latter instance the nitrone **4ad'** was formed but the intramolecular [2+3]-cycloaddition failed. We assume that in the case of **4ad'** when both the nitrone carbon and the terminal carbon of the double bond are unsubstituted the intermolecular 1,3-dipolar cycloaddition reaction may take place rather than the intramolecular one.

Based on Lumma work [1] hydrogen in the presence of a palladium catalyst was employed to cleave the N-O bond in the adducts **5aa'** and **5ac'** (Scheme 2). The hydrogenolysis of **5ac'**

[1] All new compounds were fully characterised by elemental analysis, IR, NMR and or HRMS (EI) spectra.

yielded the piperidine **6ac'** in 80% yield after column chromatography (m.p. 102-103 °C). Under these conditions **5aa'** reacted faster than **5ac'** but two products were formed: the desired piperidine **6aa'** and the acyclic by-product **6B** being the result of hydrogenolysis of benzyl-nitrogen bond followed by N-O bond cleavage; **6aa'** and **6B** were formed in the ratio 3:1, respectively. This sequence of the hydrogenolyses was deduced from the fact that the conversion of **5aa'** into the mixture of **6aa'** and **6B** required a few hours, whereas the transformation of this mixture into **6B** alone demanded long reaction time (4 days) and an additional portion of the catalyst. This result shows that the cleavage of the nitrogen-benzyl bond in **6aa'** is slow.

Scheme 2



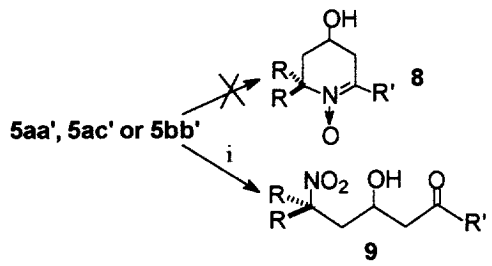
Reagents and conditions: (i) H_2, atmospheric pressure (a.p.), 10% Pd-C (Merck), MeOH, r.t., overnight; (ii) H_2, a.p., (10% Pd-C)-$NaBH_4$ (2:1, w/w), MeOH, r.t., *ca.* 5 h; (iii) 5% HClaq- MeOH (1:3, v/v), reflux 3 h, then $NaHCO_3$.

The outcomes of the hydrogenolysis were not improved by employing rhodium (5% $Rh-Al_2O_3$) or Adams platinum catalyst. However, we found out that the addition of sodium borohydride to the palladium catalyzed reduction of **5aa'** allowed the isolation of **6aa'** as an amorphous glass in 91% yield after chromatography.

We also tried to obtain the piperidine **6bb'**. In this case, to avoid reductive debromination, the zinc-acetic acid system [4-7] and molybdenum hexacarbonyl [19] were used but both attempts failed and only **5bb'** was recovered.

Acidic hydrolysis of **6aa'** afforded (±) *cis*-2,2-bis(hydroxymethyl)-4-hydroxy-2-phenyl piperidine **7** as an amorphous glass in 87% yield after column purification. The *cis* configuration of piperidine **7** was evident from its ^1H NMR spectra; the multiplet of H-4 was a wide triplet of triplets (δ=4.10 ppm, J=11.4 Hz, J=4.7 Hz) and the proton H-6 revealed as a doublet of doublets with coupling constants (δ=3.98 ppm, J=11.7 Hz, J=2.4 Hz). These data proved the axial positions of both H-4 and H-6.

Scheme 3



Reagents and conditions: (i) 60% MCPBA (3 equiv.), CH_2Cl_2, r.t.

We also examined an oxidative cleavage of the adduct **5** to obtain derivatives of 2,3,4,5-tetrahydropyridine 1-oxide **8**. By analogy to 7-oxa-1-aza-bicyclo[3.2.1]octane derivatives [20, 21] for the conversion of **5** into **8** we employed MCPBA (Scheme 3). But, in contrast to the literature data [20, 21] this reaction did not gave any nitrone **8**. The treatment of **5** with 1 equiv. of the oxidant gave a mixture in which the starting compound was the major component. Lowering the temperature to -15 °C did not help in the preparation of **8**. Only the use of 3 equiv. of MCPBA

[1] This was identified only by IR and ^1H NMR spectra.

transformed **5** completely into β-hydroxy-δ-nitroketone derivatives **9** in high yield (Table 2). Oxone® was also examined but it gave less satisfactory results than MCPBA.

The formation of **9** may be rationalized as follows: the cycloadduct **5** is oxidized to the desired nitrone **8** which reacts much faster than **5** with MCPBA to give the nitro derivative **9** *via* a nitroso intermediate. This type of the reaction of nitrones with peracids is known [22, 23] and the blue color which arose when MCPBA was added to a solution of **5** might be linked to the formation of the nitroso intermediate. However, our results are in contrast to the literature data, which report that there is no problem in stopping the oxidation of isoxazolidines at the nitrone stage [21-23].

Table 2
The yields of the derivatives **9**

Compound	Yield [%]	m.p. [°C]
9aa'	78	155-156
9ac'	64	134-135
9bb'	87	109-110

Although we did not obtain the nitrones **8**, the compounds **9** may be useful substrates for the preparation of heterocyclic derivatives through well known reactions; *e.g.* **9** might be converted into **8**, by reduction to the hydroxylamine followed by *in situ* cyclization, or into polyhydroxylated piperidines, *via* the following steps: dehydration, osmium catalyzed dihydroxylation, nitro group reduction, *in situ* cyclization and reduction of C=N bond.

In conclusion, we have shown that 4-nitro-1-butene derivatives are useful starting materials for the synthesis of highly substituted piperidines *via* the preparation of 7-oxa-1-azabicylo[2.2.1]heptane derivatives. Studies on an improvement and an extension of this methodology to highly substituted piperidine derivatives are under way.

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